

REMARKS**I. Status of the claims**

Claims 1-34, 36-69, 71-142, 144-151, 153-168 are pending in the application and stand rejected. Claims 1, 36 and 37 have been amended.

II. Amendments to the claims

Claim 36 has been amended to provide correct claim dependency. Claim 37 has been amended to remove a typographical error. Claim 1 has been amended for clarity by adding the word “and” before the last phrase. No new matter has been added.

III. Oath/Declaration

The current declaration stands objected to as being defective because non-initialed and/or non-dated alterations were made to the declaration. Applicants submit herewith a new declaration in compliance with 37 CFR 1.67(a).

IV. Rejections under 35 U.S.C. § 103**A. Papahadjopolous in view of Kikuchi and Meers**

The Examiner has rejected claims 1-16, 25, 29-31, 33, 34, 36-69, 71-81, 87-90, 99, 102-104, 106-142, 144-147 and 153-168 as being unpatentable over U.S. Patent No. 4,235,871 to Papahadjopolous et al. (“Papahadjopolous”) in view of U.S. Patent No. 4,687,661 to Kikuchi et al. (“Kikuchi”) and U.S. Patent No. 4,235,871 to Meers et al. (“Meers”). The Examiner contends that it would have been obvious to one of skill in the art at the time of the invention to combine the water miscible solvent of Kikuchi and to use the lipid of Meers (i.e., N-

acylphosphatidylethanolamines) with the teachings of Papahadjopolous. Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that “obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. “The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. Fed. Reg. Vol. 72, No. 195 at p. 57528.

The Applicants respectfully submit that the Examiner has failed to state a *prima facie* case of obviousness because there is no rational basis for the skilled artisan to modify Papahadjopolous in the manner suggested by the Examiner. Papahadjopolous describes a method of encapsulating biologically active materials in lipid vesicles. In particular, the method of Papahadjopolous *requires* the use of a water-immiscible organic solvent for forming “inverted micelles”. *Papahadjopolous* at col. 3, ll. 48-50. An aqueous mixture containing the biologically active material for encapsulation is added to the organic phase to produce a 2-phase mixture that is then emulsified. It is only when the organic phase is removed from the aqueous phase that the “inverted micelles” revert to a bilayer-like structure to form large oligolamellar vesicles containing large

amounts of aqueous phase. *Id.* at col. 3, ll. 50-53. Papahadjopolous emphasizes that emulsification and removal of the organic phase prior to final dissolution in an aqueous phase is “essential for high capture percentage in this method and is a critical difference between the process of our invention and all previous methods described.” *Id.* at col. 6, ll. 56-61. As the use of a water-immiscible organic solvent is essential to the operability of the methods of Papahadjopolous, there would be no rational basis for one of skill in the art to modify the teachings to use a *water-miscible* organic solvent as described by Kikuchi. Meers is relied on for described n-acyl phosphatidylethanolamines, and therefore, does not provide support for the use of a water-miscible solvent as claimed.

In contrast to the cited reference combination, the methods of Applicants’ claims provide for direct liposome formation using a water-miscible organic solvent that forms a single phase when mixed with an aqueous solution. Thus, emulsification and removal of the solvent is not necessary for liposome formation and high percentage capture of the biological molecule of interest.

Indeed, Papahadjopolous teaches against the use of a water-miscible organic solvent, as claimed. Applicants respectfully remind the Examiner that a reference must be considered in its entirety, for all that it teaches. Thus, a reference must be considered as a whole, including disclosures that teach away from the claimed invention. M.P.E.P. § 2142.02. Under *KSR*, “teaching away” still provides evidence of non-obviousness. *See* 127 S.Ct. at 1745. “[P]roceeding contrary to accepted wisdom in the art is evidence of nonobviousness.” M.P.E.P. §2145 (citing *in re Hedges*, 783 F.2d 1083 (Fed. Cir. 1986)). Papahadjopolous makes it clear that emulsification and removal of the water-immiscible organic solvent are required for encapsulation. “The emulsification of the initial aqueous phase into the organic phase, and the removal of the organic phase prior to the

addition of any excess aqueous phase is essential for high capture percentage in this method and is a critical difference between the process of our invention and all previous methods heretofore described.” *Papahadjopolous* at col. 6, ll. 56-61 (emphasis added). Thus, the skilled artisan, upon reading *Papahadjopolous*, would be led away from the use of a water-miscible organic solvent.

Moreover, *Papahadjopolous* indicates that the use of water-miscible organic solvents would render its invention inoperable. If when combined, the references “would produce a seemingly inoperative device,” then they teach away from their combination. *Tec Air, Inc. v. Denso Mfg. Michigan, Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999). *See also, In re Fritch*, 972 F. 2d 1260, 1265 n. 12 (Fed. Cir. 1982) (“A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose.”). As discussed above, *Papahadjopolous* states that the step of forming inverted micelles by using a water immiscible solvent and then removing the solvent prior to the addition of the excess aqueous phase is “essential for high capture.” *Papahadjopolous* at col. 6, ll. 56-61. Thus, upon reading *Papahadjopolous*, the skilled artisan would conclude that the substitution of a water miscible solvent for the water immiscible solvent would not work.

For at least these reasons, Applicants respectfully submit that *Papahadjopolous* in view of Kikuchi and Meers fails to render the presently claimed methods obvious. Withdrawal of this rejection is respectfully requested.

B. Papahadjopolous in view of Kikuchi, Meers and Epstein

The Examiner has rejected claims 17-24, 26-28, 32, 91-98, 100, 101, 105 and 148-151 as being unpatentable over *Papahadjopolous*, Kikuchi and Meers, as applied to claims 1-16, 25, 29-31,

33, 34, 36-69, 71-81, 87-90, 99, 102-104, 106-142, 144-147 and 153-168 above, and further in view of U.S. Patent No. 4,897,355 to Eppstein et al. ("Eppstein") taken with evidence of GenBank Accession No. M77788. Papahadjopolous, Kikuchi and Meers are discussed above. The Examiner relies on Eppstein to teach that liposomes could be used to encapsulate and deliver plasmid DNA or oligonucleotides; the use of the lipids such as DOPC and DPPC; methods of transfecting eukaryotic cells in vitro at 37 °C; and intravenous delivery to humans. Applicants respectfully traverse.

As discussed above, the methods of Papahadjopolous teaches against the use of water-miscible organic solvents and makes the methods disclosed therein inoperable. For the same reasons set forth above, nothing in Eppstein provides any rational basis for the skilled artisan to use a water-miscible organic solvent. Therefore, Papahadjopolous in view of Eppstein, Kikuchi and Meers fails to render the presently claimed methods obvious. Withdrawal of this rejection is respectfully requested.

C. Papahadjopolous in view of Kikuchi, Meers and Lenk

The Examiner has rejected claims 82-86 as being unpatentable over Papahadjopolous, Kikuchi and Meers, as applied to claims 1-16, 25, 29-31, 33, 34, 36-69, 71-81, 87-90, 99, 102-104, 106-142, 144-147 and 153-168 above, and further in view of U.S. Patent No. 5,169,637 to Lenk et al. ("Lenk"). The Examiner states that Papahadjopolous, Kikuchi and Meers do not specifically teach acetone, ethanol, methanol, or 2-propanol as water-miscible organic solvents. However, the Examiner relies on Lenk to disclose the aforementioned solvents and contends "[i]t would have been obvious to use acetone, ethanol, methanol, or 2-propanol because Lenk taught that these can be used to solubilize lipids. Applicants respectfully traverse.

As discussed above, Papahadjopolous teaches against the use of water-miscible organic solvents such as those solvents disclosed in Lenk. Furthermore, although Lenk describes the use of certain water miscible solvents in a process for forming liposomes, the Lenk process requires evaporation of the water/solvent mixture to form the liposome. *Lenk* at col. 9, ll. 45-55. The present claims, in contrast, provide a method of “directly” forming the liposomes, without an evaporation step. For at least these reasons, withdrawal of this rejection is respectfully requested.

V. Conclusion

In light of the amendments and remarks set forth above, Applicants submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone conference would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, Reference TRA-027.01.**

Dated: August 6, 2008

Respectfully submitted,

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